Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data

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Abstract: RATIONALE: The meta-Analysis of Cell-based CaRdiac study is the first prospectively declared collaborative multinational database, including individual data of patients with ischemic heart disease treated with cell therapy. OBJECTIVE: We analyzed the safety and efficacy of intracoronary cell therapy after acute myocardial infarction (AMI), including individual patient data from 12 randomized trials (ASTAMI, Aalst, BOOST, BONAMI, CADUCEUS, FINCELL, REGENT, REPAIR-AMI, SCAMI, SWISS-AMI, TIME, LATE-TIME; n=1252). METHODS AND RESULTS: The primary end point was freedom from combined major adverse cardiac and cerebrovascular events (including all-cause death, AMI recurrance, stroke, and target vessel revascularization). The secondary end point was freedom from hard clinical end points (death, AMI recurrence, or stroke), assessed with random-effects meta-analyses and Cox regressions for interactions. Secondary efficacy end points included changes in end-diastolic volume, end-systolic volume, and ejection fraction, analyzed with random-effects meta-analyses and ANCOVA. We reported weighted mean differences between cell therapy and control groups. No effect of cell therapy on major adverse cardiac and cerebrovascular events (14.0% versus 16.3%; hazard ratio, 0.86; 95% confidence interval, 0.63-1.18) or death (1.4% versus 2.1%) or death/AMI recurrence/stroke (2.9% versus 4.7%) was identified in comparison with controls. No changes in ejection fraction (mean difference: 0.96%; 95% confidence interval, -0.2 to 2.1), end-diastolic volume, or systolic volume were observed compared with controls. These results were not influenced by anterior AMI location, reduced baseline ejection fraction, or the use of MRI for assessing left ventricular parameters. CONCLUSIONS: This meta-analysis of individual patient data from randomized trials in patients with recent AMI revealed that intracoronary cell therapy provided no benefit, in terms of clinical events or changes in left ventricular function. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01098591.

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Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in Patients With Acute Myocardial Infarction Based on Individual Patient Data

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Rationale: **The meta-Analysis of Cell-based CaRdiac study is the first prospectively declared collaborative multinational database, including individual data of patients with ischemic heart disease treated with cell therapy.**

Objective: **We analyzed the safety and efficacy of intracoronary cell therapy after acute myocardial infarction (AMI), including individual patient data from 12 randomized trials (ASTAMI, Aalst, BOOST, BONAMI, CADUCEUS, FINCELL, REGENT, REPAIR-AMI, SCAMI, SWISS-AMI, TIME, LATE-TIME; n=1252).**

Methods and Results: **The primary end point was freedom from combined major adverse cardiac and cerebrovascular events (including all-cause death, AMI recurrance, stroke, and target vessel revascularization). The secondary end point was freedom from hard clinical end points (death, AMI recurrence, or stroke), assessed with random-effects meta-analyses and Cox regressions for interactions. Secondary efficacy end points included changes in end-diastolic volume, end-systolic volume, and ejection fraction, analyzed with random-effects meta-analyses and ANCOVA. We reported weighted mean differences between cell therapy and control groups. No effect of cell therapy on major adverse cardiac and cerebrovascular events (14.0% versus 16.3%; hazard ratio, 0.86; 95% confidence interval, 0.63–1.18) or death (1.4% versus 2.1%) or death/AMI recurrence/stroke (2.9% versus 4.7%) was identified in comparison with controls. No changes in ejection fraction (mean difference: 0.96%; 95% confidence interval, −0.2 to 2.1), end-diastolic volume, or systolic volume were observed compared with controls. These results were not influenced by anterior AMI location, reduced baseline ejection fraction, or the use of MRI for assessing left ventricular parameters.**

Conclusions: **This meta-analysis of individual patient data from randomized trials in patients with recent AMI revealed that intracoronary cell therapy provided no benefit, in terms of clinical events or changes in left ventricular function.**

Clinical Trial Registration: **URL: http://www.clinicaltrials.gov. Unique identifier: NCT01098591. (*Circ Res*. 2015; 116:1346-1360. DOI: 10.1161/CIRCRESAHA.116.304346.)**

Key Words: anterior wall myocardial infarction ■ heart failure ■ meta-analysis ■ outcome assessment ■ stem cells

Meta-analyses of randomized and cohort cell therapy studies have reported that intracoronary or intramyocardial cell delivery was safe, and it provided 2% to 8% increases in global left ventricular (LV) ejection fraction (EF) in patients with acute myocardial infarction (AMI) or ischemic cardiomyopathy.[1–4] Those meta-analyses were based on information from published articles and included different patient populations, follow-up times, and outcome measures, resulting in data heterogeneity because of inconsistent clinical definitions and parameters. In

Editorial, see p 1287
In This Issue, see p 1277

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*A full list of author affiliations and additional investigators participating in the ACCRUE database can be found in the Appendix.

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Nonstandard Abbreviations and Acronyms	
ACCRUE	meta-Analysis of Cell-based CaRdiac stUdiEs
AMI	acute myocardial infarction
CI	confidence interval
CK	creatine kinase
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
IHD	ischemic heart disease
IPD	individual patient data
LV	left ventricular
MACCE	major adverse cardiac and cerebrovascular events
TVR	target vessel revascularization

addition, publication-based meta-analyses may include studies that were later withdrawn or that contained publication errors,[5] and they may exclude important trials that reported median values of skewed data. In contrast, individual patient data (IPD)-based meta-analyses contain transparent, controlled data, with unique definitions; this approach allows analyses of specific subgroups and generation of prognostic models.

The largest previous relevant meta-analysis enrolled 50 studies (n=2625 patients). They reported that cardiac transplantation of adult bone marrow–derived cells provided persistent benefits, in terms of clinical outcome and LV parameters.[3] However, a recent meta-analysis on intracoronary cell treatment trials, which included 30 studies (n=2037 patients), could not confirm data obtained from MRI measurements of LV function[4]; moreover, they were the first to report that cell therapy had no effect on clinical outcome. Both meta-analyses used aggregated data from published studies with considerable heterogeneity across the trials involved.

The ongoing meta-Analysis of Cell-based CaRdiac study (ACCRUE; NCT01098591, formerly MEta-analysis of Stem cell Studies, MESS) is a collaborative, multinational database that comprises IPD from randomized and cohort studies. The ACCRUE database was established to facilitate exploration of the clinical safety and efficacy of cell therapy in patients with ischemic heart disease (IHD) and to identify subgroups of patients predicted to benefit from cell therapy. The present study represents the first IPD-based meta-analysis of cell treatment in IHD to date. The objectives of the ACCRUE database are as follows:

1. To estimate the overall treatment effect of cardiac cell-based therapy on clinical outcomes, including occurrence of major adverse cardiac and cerebrovascular events (MACCE, composite of all-cause death, AMI recurrence, coronary target vessel revascularization [TVR], and stroke) and the occurrence of clinical hard end points (death, AMI recurrence, or stroke);
2. To analyze the effect of cell treatment on LV function and remodeling, including changes in end-diastolic volume (EDV), end-systolic volume (ESV), and EF;
3. To identify predictors of MACCE and of LV function and remodeling improvements in patients with IHD treated with cell therapy;
4. To explore the influence of patient characteristics, including cardiovascular risk factors, on the safety and efficacy of cardiac cell therapy;
5. To identify the characteristics of individual patients with IHD, that can predict benefit from cell therapy.

Methods

The main objective of the ACCRUE group is to use IPD to improve the quality of data used in meta-analyses of cell therapy studies in patients with chronic IHD and AMI. The first collaborative meeting was held in Vienna, 2007, with the investigators of the ASTAMI, REGENT, BOOST, Aalst (Bartunek)-study, BONAMI, REPAIR-AMI, Atsma-study, MYSTAR, STEMMI, the Hamburg and Novosibirsk intramyocardial studies, and the EUROINJECT-ONE cardiac gene therapy study. The meeting aimed to define objectives, to establish data contribution criteria, and to appoint the Independent Data Committee and Steering Committee (Online Data Supplement).

Criteria for Considering Studies for Inclusion in the ACCRUE Database

The criteria for participation in the ACCRUE database were that the data must be from randomized or cohort clinical studies, and that cardiac regeneration was induced by percutaneous administration of cells or cell-based products, or by mobilization of bone marrow–derived cells. A continuous literature search was initiated, and principal investigators and study coordinators of recently published studies were prospectively invited to contribute IPD to the database. Additional study inclusion criteria for randomized studies are included in the Online Data Supplement.

Outcome Measures

The primary outcome measure of the ACCRUE meta-analysis was the safety of the treatment, defined as the freedom from MACCE (the composite of all-cause death, AMI recurrence, stroke, and TVR). The secondary end points were freedom from the combined hard clinical end points (all-cause death, AMI recurrence, or stroke) or freedom from the individual components of MACCE. Another secondary end point was efficacy, defined as changes in LV EDV, ESV, and EF, compared with baseline.

Search Methods for Identifying Studies

Studies were prospectively identified in literature searches, and the identified investigators were invited to participate. The search methods are included in the Online Data Supplement.

Data Collection and Management

The data collection method is described in the Online Data Supplement. The corresponding authors and primary investigators of the selected studies were e-mailed or contacted personally several times with invitations to contribute original data to the central database (Figure 1). A database with predefined terms and conditions (determined and agreed on at the first investigator meeting) was sent to the participants for depositing the individual data. Authors from 39 centers responded, and data were received from 23 centers[6–17] (References 18–28 in the Online Data Supplement). One center later cancelled participation and withdrew their data, referencing changes in institutional policy. The current ACCRUE database comprises 1871 IPD sets from 28 studies (15 randomized and 10 cohort cell therapy and 3 granulocyte-colony stimulating factor studies). All patients were classified as “cell-treated” (n=1203) or “control” (n=668).

In accordance with prespecified plans, analyses performed in ACCRUE differ from those performed in the individual papers. Therefore, results from the ACCRUE report may be different from those reported in the individual papers, particularly when different terms were used for event classifications or follow-up times. These issues were discussed with the corresponding authors of all papers.

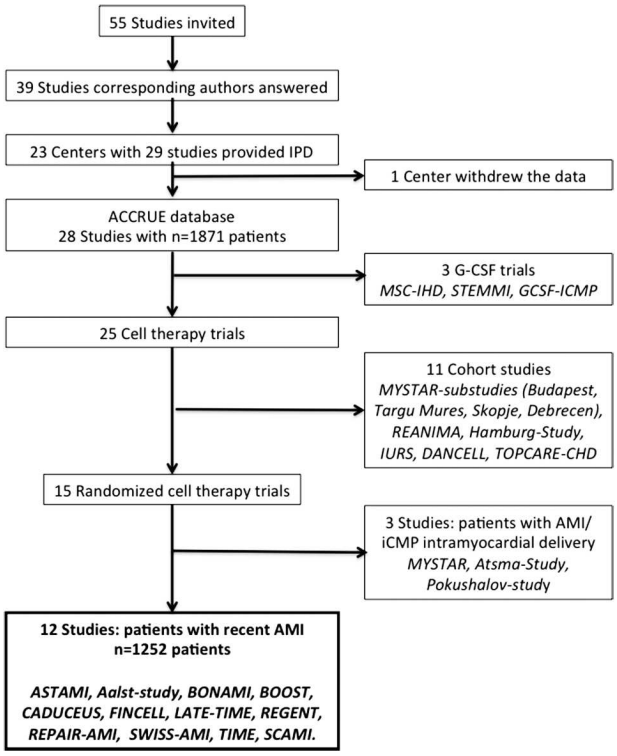

Figure 1. Flow diagram of the meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) database and participating studies. AMI indicates acute myocardial infarction; G-CSF: granulocyte colony-stimulating factor; iCMP: ischemic cardiomyopathy; and IPD, individual patient data.

All studies were approved by the local ethics committees. Additional approval was obtained for the meta-analysis. Data quality was evaluated with quality checklists from CONSORT[18] and PRISMA (http://www.prisma-statement.org) statements and guidelines.

The database was controlled by the IDC. It was temporarily closed in June 2014, to perform the first statistical analysis. The current meta-analysis included data from patients with recent AMIs who were randomized to either intracoronary cell therapy or control groups (ASTAMI, Aalst, BONAMI, BOOST, CADUCEUS, FINCELL, LATE-TIME, REGENT, REPAIR-AMI, SWISS-AMI, TIME, SCAMI trials).[6–17] The present analysis excluded all noncontrolled studies, the MYSTAR study with a combined delivery mode, and all randomized percutaneous intramyocardial cell-based studies in patients with chronic IHD (Figure 1).

Assessment of Risk of Bias in Included Studies

Methods for assessing the risk of bias and quality assessment are described in the Online Data Supplement.

Statistics

This IPD meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Intervention[19] and the guidelines for meta-analysis of IPD for time-to-event outcomes.[20,21] Heterogeneity between the studies was tested with I^2 statistics. Additional sensitivity analyses were performed to detect differences between studies. Two investigators conducted the analyses (E.N., M.G.).

Investigation of Heterogeneity and Selection Bias

The statistics for investigating heterogeneity and selection bias of the included trials are presented in the Online Data Supplement.

General Statistics

Normally distributed, continuous variables are presented as mean±SD. Continuous parameters with skewed distributions are expressed as the median and first interquartile range. Binary and categorical variables are given as frequencies and percentages. Associations between the number of cells/log number of cells and the changes in EDV, ESV, or EF in the cell-treated group were calculated with linear regression analysis.

All P values were based on 2-sided tests. For multiple comparisons, P values <0.01 were considered statistically significant.

IPD Meta-Analysis

All analyses were based on the intention to treat. Multiple Cox regression models were used to analyze the primary outcome, stratified for the individual studies. The multiple models included cardiovascular prognostic factors for the occurrence of MACCE, such as sex, age, diabetes mellitus, hypertension, hyperlipidemia, and baseline EDV and EF values. This

Table 1. Study Characteristics

Name of Study	Sample size (Cell Therapy/Controls)	Mean Follow-Up Duration, mo	Cell Type	Location of AMI	Time From AMI to Cell Delivery, d	Imaging Modality
CADUCEUS	17/8	12	Cardiosphere-derived cells	Anterior (except 1)	62±11	MRI
BONAMI	52/49	3	BM-MNC	Anterior	9±2	SPECT, RNV
Aalst Study	19/16	4	BM-MNC	Multiple	12±1	LV angiography
REPAIR-AMI	101/103	4	BM-MNC	Multiple	4±1	LV angiography
BOOST	30/30	6	BM-MNC	Multiple	5±1	MRI
LATE-TIME	58/29	6	BM-MNC	Multiple	17±5	MRI
ASTAMI	50/50	6	BM-MNC	Anterior	6±1	SPECT, echocardiography
REGENT	160/40	6	BM-MNC, or selected CD34+CXCR	Anterior	7±2	MRI
SWISS-AMI	133/67	4	BM-MNC	Multiple	13±10	MRI
TIME	79/41	6	BM-MNC	Multiple	5±2	MRI
SCAMI	29/13	12	BM-MNC	Multiple	6±1	MRI
FINCELL	39/39	6	BM-MNC	Multiple	3±1	Echocardiography

AMI indicates acute myocardial infarction; BM-MNC, bone marrow mononuclear cells; LV, left ventricular; RNV: radionuclide ventriculography; and SPECT, single photon emission computed tomography.

Table 2. Baseline Data of Patients With Recent Acute Myocardial Infarction and Randomized to Cell Therapy or Control

	Cell Therapy (n=767)	Control (n=485)	*P* Value
Baseline			
Age, y	57.3±10.4	57.0±10.7	0.600
Men	614/767 (80.1%)	405/485 (83.5%)	0.136
Diabetes mellitus	111/767 (14.5%)	79/485 (16.3%)	0.419
Hypertension	384/767 (50.1%)	244/485 (50.3%)	0.954
Hyperlipidemia	387/717 (54.0%)	228/435 (52.4%)	0.626
Active smoker	396/708 (55.9%)	243/422 (57.6%)	0.620
Maximal creatine kinase, U/L	3467±2492	3410±2426	0.235
Number of diseased vessels	1.3±0.6	1.3±0.6	0.952
Anterior AMI	662/767 (86.3%)	415/485 (85.6%)	0.351
Precell therapy			
End-diastolic volume, mL	146±51	139±48	0.012
End-systolic volume, mL	84±40	77±36	0.004
Ejection fraction, %	43.7±11.9	45.5±11.8	0.011
MRI	492/767 (64.1%)	257/485 (53.0%)	<0.001
Cell therapy			
Time from AMI to treatment in cell therapy group and randomization/sham intervention in controls, d	8.0±9.7	6.6±10.9	0.202
Number of cells injected intracoronary ($\times 10^6$) (median and 25% and 75% interquartile ranges)	150 (6, 294)		
Intracoronary injection-related procedural complication, %	14/630 (2.2%)		
In-hospital complication, %	21/631 (3.3%)	21/413 (5.1%)	0.197

AMI indicates acute myocardial infarction.

model was used to determine an adjusted, common treatment effect, with baseline hazards that varied across studies.[20,21] To evaluate possible dependencies of the treatment effect on other prognostic factors, all possible interactions were tested within the multiple stratified Cox regression models. Factors were excluded from the analysis when data were missing in ≥50% of cases (eg, positive family anamnesis for heart disease, baseline infarct size). Adjusted hazard ratios and their 95% confidence intervals (CIs) are presented with the corresponding *P* values. The Kaplan–Meier method and cumulative hazards were used to display the MACCE-free, death-free, death/AMI recurrence/stroke-free, and TVR-free survival rates. Prespecified subgroup analyses for the primary end point and the secondary end point of death/AMI recurrence/stroke were performed for the following subgroup categories: age (> or ≤57 years), EF (> or ≤45%), baseline EDV (> or ≤130 mL), anterior AMI (yes or no), maximal creatine

Table 3. Primary and Secondary End Points

	Cell Therapy (n=767)	Control (n=485)	*P* Value
Follow-up			
Follow-up time, d	225±112	231±114	0.375
Median with range	(180; 90–365)	(180; 90–365)	
MACCE	107/767 (14.0%)	79/485 (16.3%)	0.289
All-cause death	11/767 (1.4%)	10/485 (2.1%)	0.499
Target vessel revascularization	87/767 (11.3%)	65/485 (13.4%)	0.287
Death or AMI recurrence or stroke	22/767 (2.9%)	23/485 (4.7%)	0.088
Non-serious adverse events	55/680 (6.5%)	40/472 (8.5%)	0.206
End-diastolic volume, mL	162±57	153±54	0.008
End-systolic volume, mL	89±48	82±44	0.012
Ejection fraction, %	47.3±13.9	48.3±13.4	0.245
Changes from baseline to follow-up	(n=624)	(n=440)	
ΔEnd-diastolic volume, mL	15.0±40.1	13.8±33.4	0.614
Mean difference (SE), 95% CI	1.2 (2.3), –3.4 to 5.8		
ΔEnd-systolic volume, mL	5.0±32.5	4.6±27.4	0.853
Mean difference (SE), 95% CI	0.4 (1.9), –3.4 to 4.1		
ΔEjection fraction, %	3.6±9.5	2.6±8.9	0.096
Mean difference (SE), 95% CI	0.96 (0.58), –0.2 to 2.1		

AMI indicates acute myocardial infarction; and MACCE, major adverse cardiac and cerebrovascular events.

kinase (CK, > or ≤3450 U/L; CK is associated with infarct size; 3450 U/L was the median value for all patients), sex, diabetes mellitus, hypertension, hyperlipidemia, smoking, and use of MRI.

The secondary end points, changes in LV EF, EDV, and ESV, were evaluated with ANCOVA. The treatment effect was adjusted for cardiovascular risk factors, men, mode of measuring LV function, anterior location of AMI, baseline EDV, baseline EF, and time between AMI and randomization/sham intervention in controls or cell therapy in cell-treated groups; for these adjustments, the individual studies were considered a block factor. Possible interacting effects with treatment were tested within these ANCOVA models. Changes in EDV, ESV, and EF in the cell therapy and control groups are expressed as mean±SD; the mean difference from baseline was reported with SE and the relative 95% CIs were reported as effect measures.

Prespecified subgroup analyses included the effect of follow-up time and the effect of baseline EF on changes in LV function, evaluated as dichotomous variables. The numbers of patients in groups who received different subtypes of autologous cells were uneven or low; therefore, we did not perform subgroup analyses on the effect of cell types on the end points.

All statistical computations were performed with Review Manager 5.2 (The Nordic Cochrane Center, Købehvn, Denmark), and Stata/SE, version 12, for Windows (StataCorp, Houston, TX).

Results

Search Results

A systematic search for eligible trials resulted in 1533 clinical reports on cardiac cell therapies. Of these, 921 were excluded on the basis of the preclinical nature of the studies or because they were only abstracts or incomplete reports. Thus, 612 clinical studies were eligible, and 149 were selected because they used cell injections or autologous bone marrow–derived cells mobilization. A further 94 studies were excluded because they were reviews, descriptions of surgical approaches, or pilot studies for study designs or subanalyses. Finally, 55 studies were selected, and the corresponding authors were contacted. The present analysis included 12 randomized studies on intracoronary cell therapy applied after AMI (Figure 1).

Study Characteristics

Table 1 lists the study characteristics. An average of 104 patients were included in the studies (n=64 and n=40 for cell treatment and control groups). Most studies used bone marrow mononuclear cells, and MRI was used for visualizing and quantifying LV performance. Three studies assessed the timing of cell therapy (CADUCEUS, LATE-TIME,

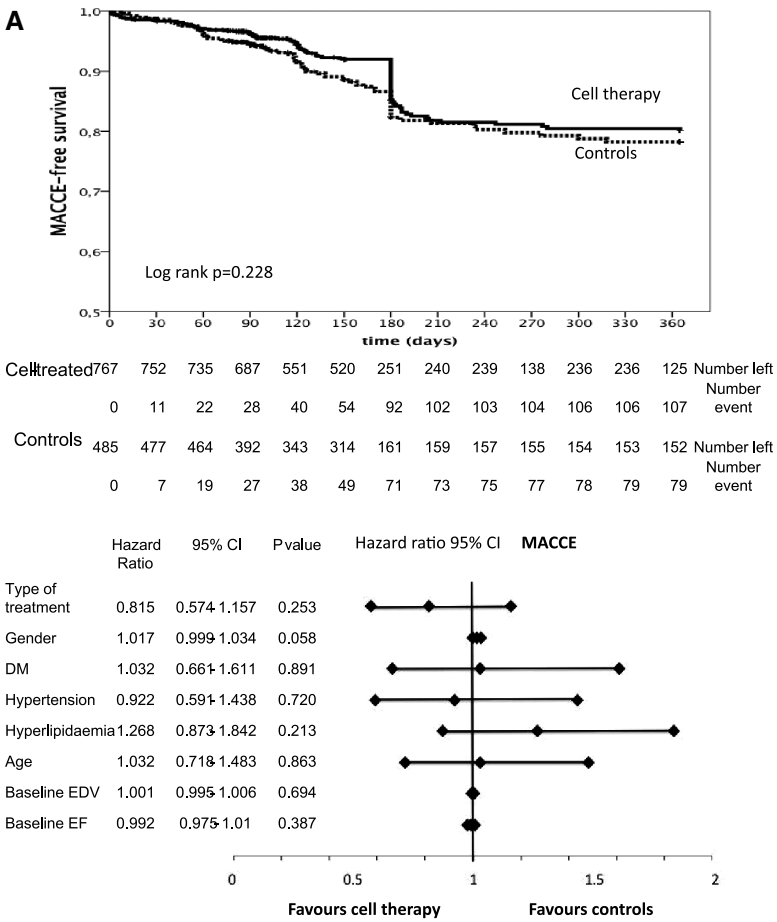

Figure 2. Primary end point analysis. A, Major adverse cardiac and cerebrovascular events (MACCE)-free survival of patients with recent acute myocardial infarction who were randomized to either cell therapy or control treatment (**top**). Hazard ratio and 95% confidence intervals (CI) of risk factors that favor cell therapy or control treatment (**bottom**). MACCE defined as all-cause death, reinfarction, target vessel revascularization, and stroke; DM indicates diabetes mellitus; EDV, end-diastolic volume; and EF, ejection fraction. **B,** Forest plot of MACCE-free survival in subgroups, with creatine kinase (CK), CI, hazard ratio (Haz), and *P* for interaction (*P* inter).

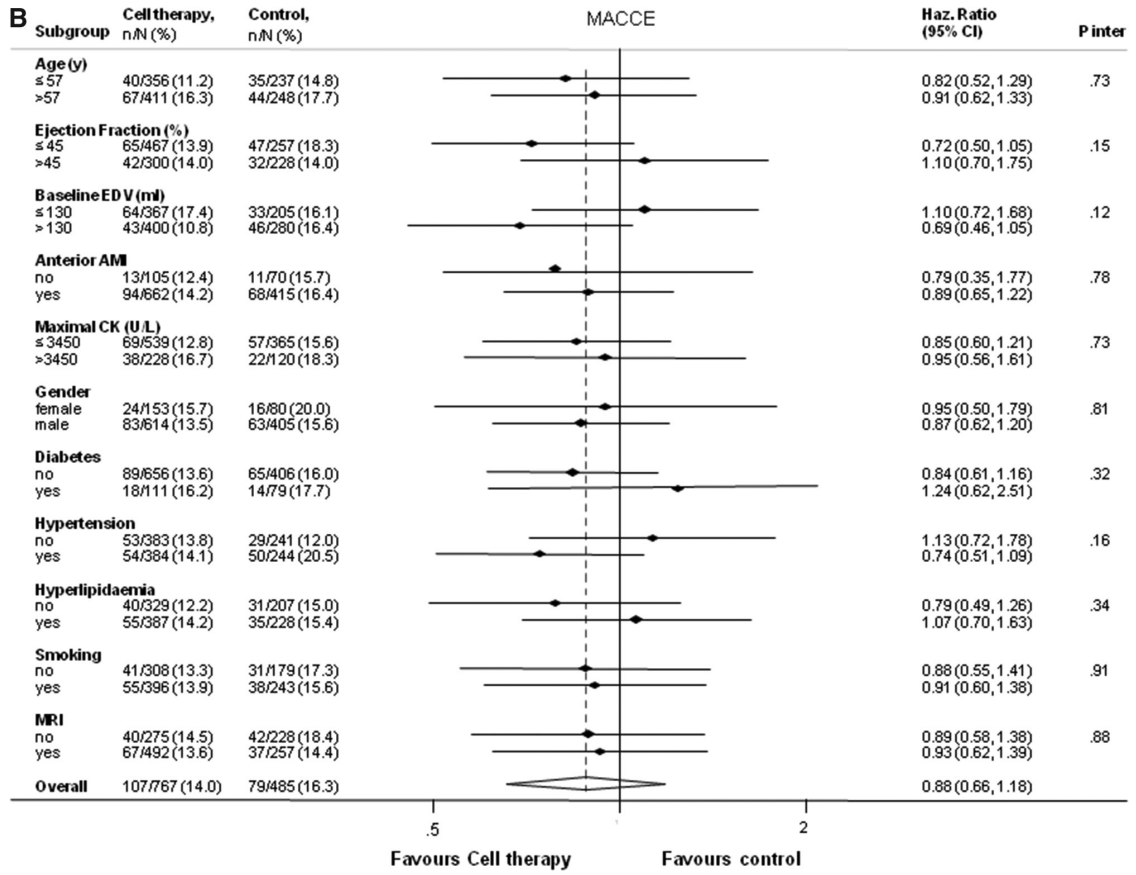

Figure 2. Continued

SWISS-AMI); otherwise cell therapies were performed within 2 weeks post-AMI. Most patients were randomized during the first week (65% of patients in the cell therapy and 79% of patients in the control group), and EF was measured before randomization. The quantitative baseline LV functional parameters were assessed at the time of the primary percutaneous coronary intervention (eg, FINCELL), before randomization, 1 to 3 days post-AMI (eg, REGENT), or several weeks post-AMI after resolution of myocardial stunning (eg, LATE-TIME). Thus, there were different time lapses between the delivery of cell therapy and the measurement of baseline LV function.

All patients received clinical follow-ups. Paired LV functional data measured at baseline and at follow-up were available for 1064 (624 cell therapy and 440 control) patients. Baseline LV function and follow-up events were not different for patients who lacked paired LV data for any reason (data not shown).

Infarct size data were available for 114 of 767 patients (14.9%) who received cell therapy and for 111 of 485 patients (22.9%) in the control group. Because these groups did not represent the entire population, we did not analyze changes in infarct size.

Study Quality and Risk of Bias in Included Studies

Online Table I shows the quality assessment scales of the studies on randomized intracoronary cell therapy in AMI that were included in the ACCRUE database. The internal validity scales, the results of the external validity criteria, and sensitivity analyses are described in Online Data Supplement.

Baseline Patient Characteristics

Table 2 shows the baseline clinical data, including measurements of baseline LV function parameters. No differences were observed between the 2 groups with the exception of ESV, which was lower in controls. Cardiac MRI was more often used as the imaging modality in the cell therapy group because of the higher number of patients in cell therapy group than in the control groups of the SWISS-AMI and REGENT trials (2:1 randomization).

Primary End Point

MACCE was similar between the groups (hazard ratio, 0.86; 95% CI, 0.63–1.18; Table 3; Online Figure I). After adjusting for all confounding factors, the Cox regression showed no effect of cell therapy on MACCE-free survival (Table 3; Figure 2). The addition of anterior AMI as a confounding factor did not influence the primary outcome (Online Table II). The subgroup analysis did not reveal a prognostic factor for prevention of MACCE (Figure 2); therefore, we found no factors that influenced the success of cell therapy.

The results of the overall meta-analysis (between-trial analysis) for the primary end point were highly consistent in direction and magnitude with those obtained from the individual participant data meta-analyses (within-trial analyses); ie, there was no significant benefit with cell therapy versus controls (hazard ratio, 0.86; 95% CI, 0.63–1.18; P=0.884). No

significant heterogeneity or inconsistency was found between trials (I^2=0%). In addition, the funnel plot for the primary end point did not show asymmetry on visual inspection (Online Figure I), which was confirmed by a nonsignificant Egger test.

Secondary End Points

Similar to the primary end point, cell therapy did not improve clinical outcome in terms of the incidence of death, or death/AMI recurrence/stroke, and TVR (Table 3; Figure 3A, Online Figure II). No cardiovascular risk factor could be identified that influenced the clinical hard end points (death/AMI recurrence/stroke). Similarly, the hard end points were not impacted by a lower baseline EF, a higher EDV, the location of infarction, the maximal CK, or whether LV function was measured with MRI. Although we observed a trend toward differences in different subgroups, as shown in the forest plot (Figure 3B), no interaction was significant (P>0.01).

Both EDV and EF increased slightly in cell-treated and control groups (Table 3) without a decrease in ESV from baseline to follow-up. Cell therapy did not influence the changes in global EF (mean between-group difference of 0.96%; 95% CI, −0.2 to 2.1), EDV (1.2 mL; 95% CI, −3.4 to 5.8), or ESV (0.4 mL; 95% CI, −3.4 to 4.1; Table 3; Figure 4).

Table 4 summarizes the ANCOVA results (detailed data in Online Table III). The final changes in EDV, ESV, and EF were not influenced when the model included covariates of sex, age, diabetes mellitus, hypertension, hyperlipidemia, anterior AMI location, MRI imaging modality, baseline EDV, baseline EF, or timing of cell treatment. Cell therapy in older patients led to a greater increase in EDV compared with controls, with no significant changes in ESV or EF (Online Table III).

Subanalysis of Different Follow-Ups

Four studies provided a 1-year clinical follow-up data (CADUCEUS, REPAIR-AMI, SWISS-AMI, and SCAMI); the other studies reported clinical follow-ups of ≤6 months. No difference between the groups was identified at the 6-month follow-ups or at the 6- to 12-month follow-ups on MACCE, death, death/AMI recurrence/stroke, or TVR (Online Figures III–V). The majority of MACCE events were TVR at the 6-month follow-up. Trials with a planned 6-month clinical follow-up controlled the patients and performed TVR

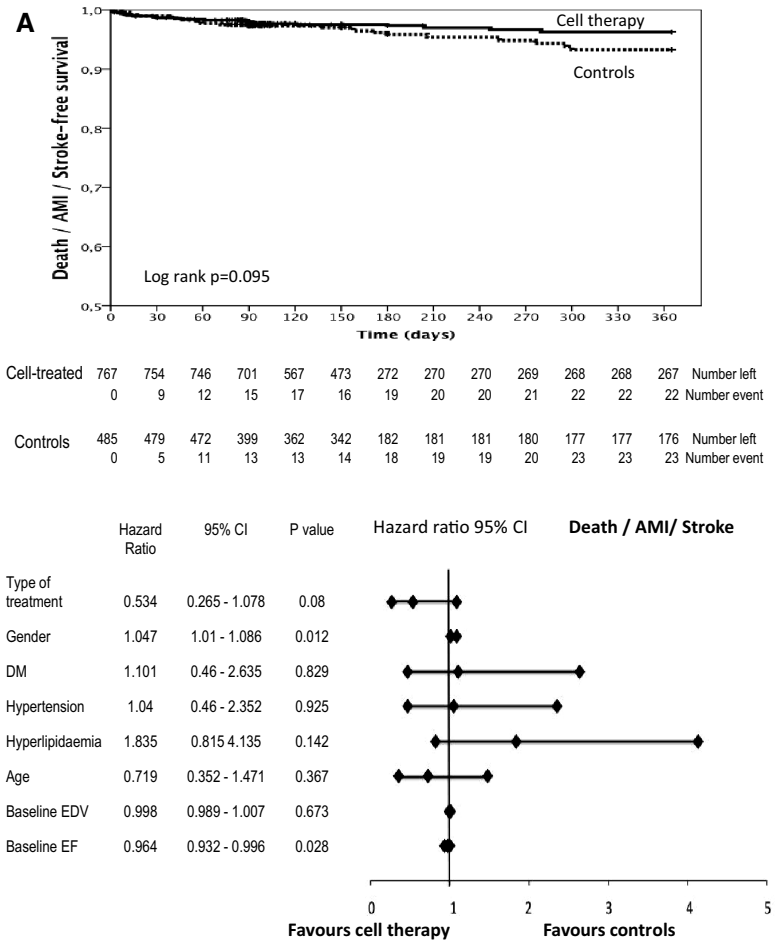

Figure 3. Secondary end point analysis. A, Kaplan–Meier analysis of death/acute myocardial infarction (AMI)/stroke–free survival of patients randomized either to cell therapy or controls (**top**). Hazard ratio (Haz) and 95% confidence intervals (CI) of risk factors favoring cell therapy or control treatment (**bottom**). DM indicates diabetes mellitus; EDV, end-diastolic volume; and EF, ejection fraction. **B,** Forest plot of death/AMI/stroke-free survival in subgroups with hazard ratio, CI, *P* for interaction (*P* inter), and CK, creatine kinase. **C,** Kaplan–Meier analysis of target vessel revascularization (TVR)-free survival (**top**). Hazard ratio and 95% CIs of risk factors favoring cell therapy or control treatment (**bottom**).

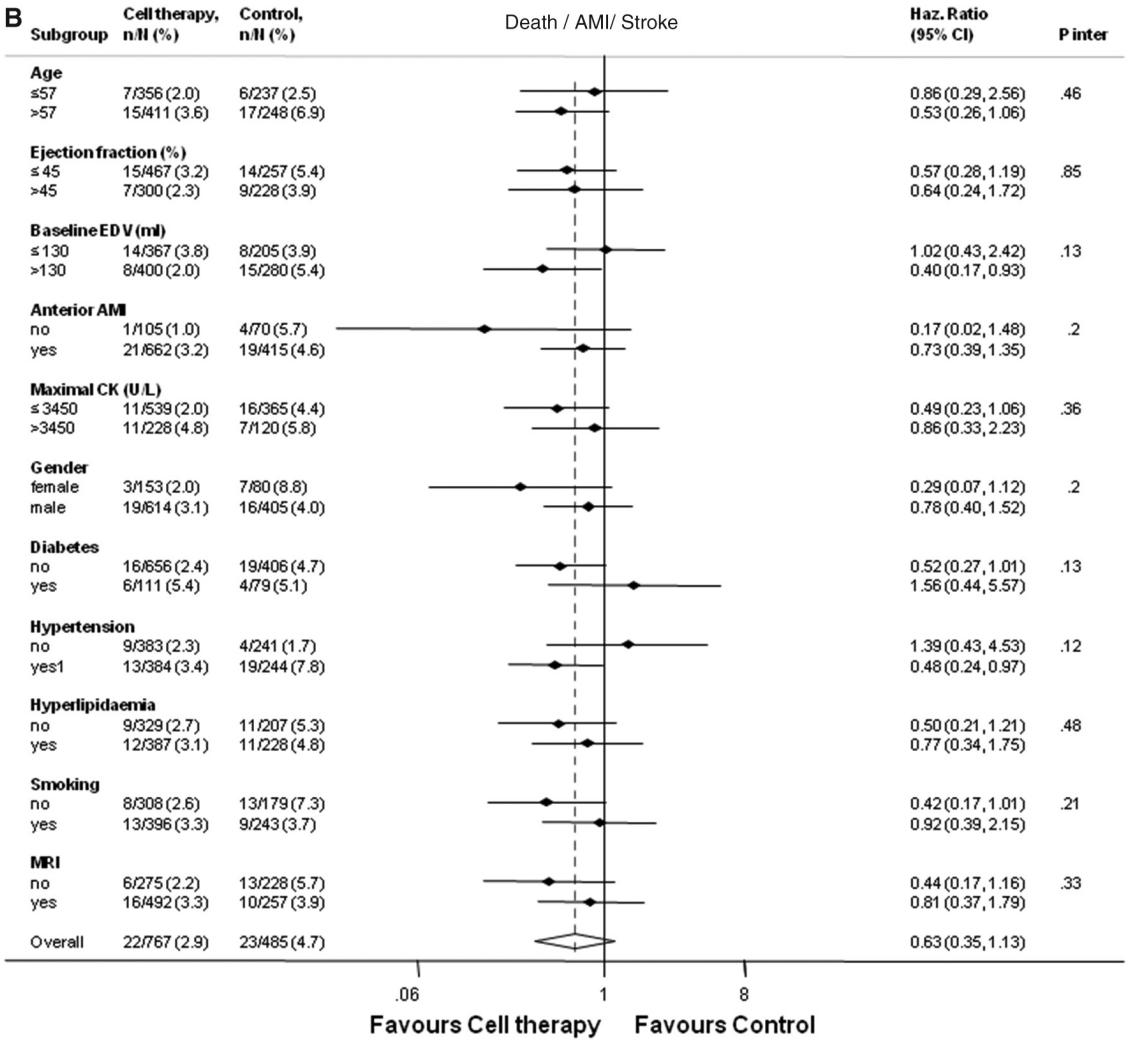

Figure 3. Continued

when in-stent restenosis of the infarct-related artery was documented. This resulted in an increase in the TVR incidence at 6 months, but there was no difference between groups.

Most of the LV functional measurements were performed at the 6-month follow-up; the Aalst-study, BONAMI, and REPAIR-AMI provided 3- or 4-month follow-up data; the CADUCEUS and SCAMI studies also had control measurements at 1 year. Table 5 shows the follow-up time-dependent changes in LV EDV, ESV, and EF in cell-treated and control groups. An increase was observed in EDV from baseline to the 6-month and 12-month follow-ups in both the cell therapy and control groups. Because of the relatively low numbers of patients in these subgroups, and to avoid a type I error, we did not perform statistical comparisons between the 6- and 12-month follow-up data. No difference between groups was detected on follow-up data collected at ≤6 months, or >6 months.

Subanalysis of Baseline EF Effects on Changes in LV Parameters

The subclasses of baseline EF (>50%, >45%, and >40%) showed no influence of baseline EF on the changes in EDV, ESV, or EF at the follow-up (Table 6).

Effect of the Number of Injected Cells on LV Function

Linear regression analysis showed no correlation between the number of injected cells or the log number of injected cells and the changes in EDV, EF (Online Figure VI), or ESV (data not shown) in the cell-treated group. There was, however, a large scatter in the number of cells applied (range: 12.5–4303×10^6).

Comparison of ACCRUE Data With Results From Nonparticipating Studies

Online Table IV summarizes the results from currently published randomized cell-therapy trials in patients with recent AMI who did not contribute to the ACCRUE database. The reported mean EF, SD, and the number of included patients are shown (References 29–47 in the Online Data Supplement). These 19 studies included 503 patients (mean=27) in the cell-treated group and 352 patients (mean=19) in the control group. In contrast, the ACCRUE intracoronary arm included 767 patients (mean=64) in the cell-treated group and 485 patients (mean=40) in the control group. The ACCRUE database currently represents >70% of all clinical cardiac regeneration

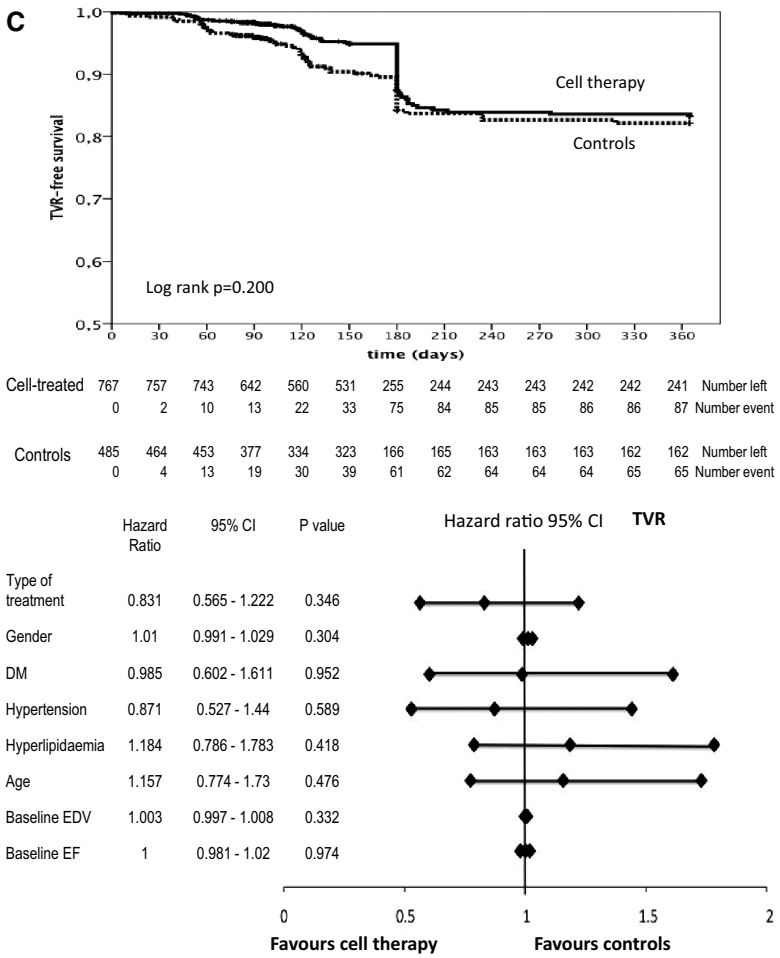

Figure 3. Continued

studies and ≈60% of all intracoronary cell studies; it includes all major randomized studies, except the HEBE trial, the Cao, and the Chen studies (References 36, 40, and 45 in the Online Data Supplement).

Discussion

The ACCRUE is the first IPD database to facilitate meta-analyses of cardiac cell therapy. The database currently comprises a pool of 1871 IPD from 15 randomized cardiac regeneration studies; 12 of these studies (with 1252 IPD) involved intracoronary cell delivery in patients with recent AMIs. This first meta-analysis of the ACCRUE selecting these 12 randomized studies on intracoronary administration of reparative cells shows no effect of cell therapy on clinical events or changes in LV function or remodeling. On the basis of original data, we could not identify predictive factors or patient characteristics that might indicate patients most likely to benefit from cell therapy.

An important feature of this ACCRUE, which is rarely seen in other meta-analyses, is its prospective nature, following the Cochrane guidelines for planning and conducting an IPD meta-analysis. The prospective data collection of ACCRUE allows the uniform definitions of end points, follow-up periods, and adverse events; this approach ensured the most unbiased, and thus, the most reliable results, and increased the robustness and accuracy of the findings.

However, some caution should be taken with the interpretation of our results. The negative and, for the health community, disappointing results are not surprising. Six of the included studies (including about two thirds of the study patients), which comprised the largest and most homogeneous clinical populations (ASTAMI, BONAMI, REGENT, TIME, LATE-TIME, SWISS-AMI), reported no benefit from autologous cell-based, intracoronary regenerative treatment.[8,9,11,15–17] One of the 3 similarly large studies which were not included in the ACCRUE database (HEBE) also reported a negative outcome.

Potentially, the efficacy of cell therapy could be affected by differences among the studies included in the ACCRUE database. For example, differences in the types of injected cells and the timing of cell administration (acute phase of AMI versus convalescent AMI) may affect the outcomes. We did not evaluate these factors separately because the individual subgroups would have comprised statistically unacceptably low number of patients. However, the ANCOVA analysis showed that, when the time to cell/control therapy was considered as an independent covariate, it did not significantly affect the changes in EDV, ESV, or EF. An additional factor that might influence changes in LV function could be the time

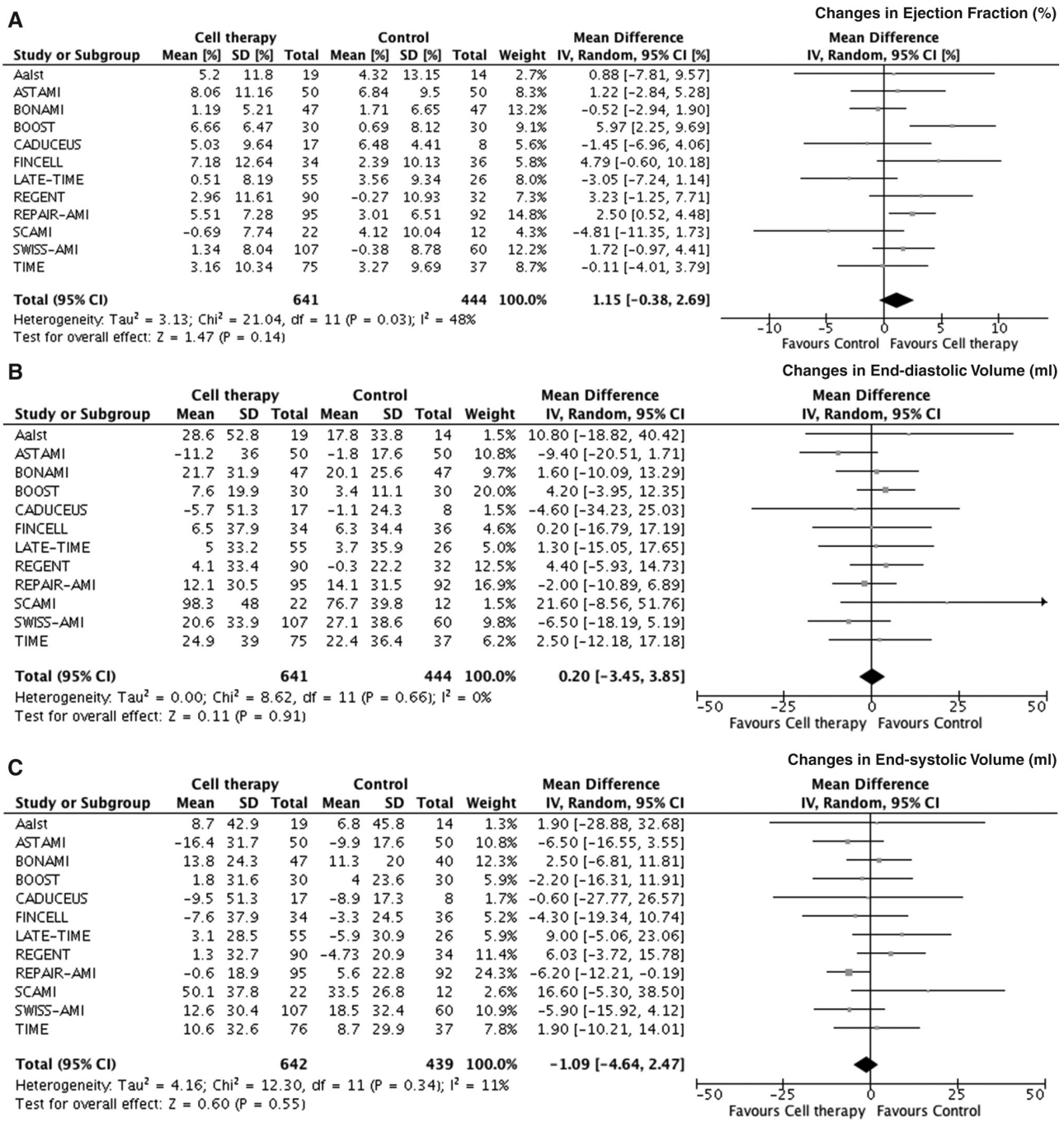

Figure 4. Forest plot displaying changes in left ventricular ejection fraction, end-diastolic and end-systolic volumes in patients treated with intracoronary cell therapy after recent acute myocardial infarction. Unadjusted difference in mean with 95% confidence intervals (CI). **A**, Forest plot of changes in ejection fraction. **B**, Forest plot of changes in end-diastolic volumes. **C**, Forest plot of changes in end-systolic volumes.

that baseline EF was measured (if not the same day as the cell therapy). This timing may be consequential, considering that, in the natural course of the reperfused AMI, during the first week, rapid changes were observed in the EF, and the size of late enhancement in serial MRI.[22] Moreover, there was a time-dependent component in the regenerative function of the different types of harvested autologous comorbid bone marrow–origin cells.[23]

Adverse Events, LV Function, and LV Remodeling Related to Intracoronary Cell Therapy

Intracoronary administration of cells proved to be safe, with a low procedural complication rate (2.2%). The composite in-hospital complications were similar between groups. The mortality and incidence of hard clinical end points were noticeably low among the patients with ST-segment–elevation myocardial infarction in both groups. This finding may have

Table 4. Results of Interaction Analysis (ANCOVA Models) in Patients With Recent Acute Myocardial Infarction and Randomized Either to Cell Treatment of Controls

	Changes in EDV	Changes in ESV	Changes in EF
Cell treatment effect with men			
P value	0.919	0.977	0.091
Mean difference	−0.32	−0.08	1.34
SE (95% CI)	3.2 (−6.6 to 5.9)	2.6 (−5.2 to 5.1)	0.79 (−0.2 to 2.9)
Cell treatment effect with diabetes mellitus			
P value	0.483	0.694	0.388
Mean difference	2.30	1.06	0.70
SE (95% CI)	3.3 (−4.1 to 8.7)	2.7 (−4.2 to 6.3)	0.8 (−0.9 to 2.3)
Cell treatment effect with hypertension			
P value	0.603	0.852	0.092
Mean difference	1.22	0.36	0.98
SE (95% CI)	2.3 (−3.4 to 5.8)	1.9 (−3.4 to 4.1)	0.6 (−0.2 to 2.1)
Cell treatment effect with hyperlipidemia			
P value	0.430	0.738	0.067
Mean difference	1.95	0.67	1.09
SE (95% CI)	2.5 (−2.9 to 6.8)	2.0 (−3.3 to 4.6)	0.6 (−0.1 to 2.3)
Cell treatment effect with MRI			
P value	0.604	0.887	0.028
Mean difference	1.26	−0.28	1.31
SE (95% CI)	2.4 (−3.5 to 6.0)	2.0 (−4.2 to 3.6)	0.6 (0.1 to 2.5)
Cell treatment effect with age			
P value	0.006	0.029	0.702
Mean difference	9.50	6.46	0.35
SE (95% CI)	3.4 (−2.8 to 16.2)	2.9 (−0.7 to 12.2)	0.9 (−1.5 to 2.2)
Cell treatment effect with anterior infarction			
P value	0.737	0.448	0.074
Mean difference	−1.11	−2.05	1.47
SE (95% CI)	3.3 (−7.6 to 5.4)	2.7 (−7.4 to 3.3)	0.8 (−0.1 to 3.1)
Cell treatment effect with pre-end-diastolic volume			
P value	0.408	0.867	0.238
Mean difference	1.46	0.26	0.76
SE (95% CI)	1.8 (−2.0 to 5.0)	1.5 (−2.8 to 3.3)	0.6 (−0.5 to 2.0)
Cell treatment effect with pre-ejection fraction*			
P value	0.418	0.793	0.304
Mean difference	1.69	0.51	0.76
SE (95% CI)	2.1 (−2.4 to 5.8)	1.9 (−3.1 to 4.3)	0.7 (−0.7 to 2.2)
Cell treatment effect with time to cell therapy†			
P value	0.649	0.938	0.435
Mean difference	7.78	8.92	−0.73
SE (95% CI)	4.9 (−1.9 to 17.5)	4.0 (1.1–16.8)	1.2 (−1.6 to 3.1)

CI indicates confidence interval; EDV, end-diastolic volume; EF, ejection fraction; and ESV, end-systolic volume.

*Subanalysis between pre-EF groups are displayed in Table 6.

†Effect of the covariate time to cell therapy in cell therapy group or randomization/sham intervention in controls post-AMI.

resulted from the carefully selected patients and the relatively high baseline EFs. Subanalyses of different follow-ups did not change the outcome difference between treated and control patients; the negative results were consistent. We point out that a placebo effect has been observed in blinded randomized trials, although this effect might be less significant than in nonrandomized studies. Because the placebo effect is additive to the control treatment effect, it can reduce

Table 5. Efficacy of Cell Therapy Compared With Time

Follow-Up Time		Changes in EDV (Mean±SD)	Changes in ESV (Mean±SD)	Changes in EF (Mean±SD)
≤6 Months	Cell therapy (n=383)	10.2±37.3	2.2±32.6	3.9±10.3
	Controls (n=267)	8.4±28.8	0.31±26.2	2.9±9.6
	Difference in mean (95% CI)	1.9 (–3.4 to 7.2)	1.9 (–2.9 to 6.6)	0.9 (–0.6 to 2.5)
>6–12 Months	Cell therapy (n=241)	22.4±43.3	9.3±32.0	3.1±8.1
	Controls (n=173)	22.2±37.9	11.3±28.0	2.1±7.8
	Difference in mean (95% CI)	2.6 (–7.8 to 8.3)	–2.0 (–8.0 to 4.0)	1.0 (–0.6 to 2.5)

No significant difference between the groups. CI indicates confidence interval; EDV, end-diastolic volume; EF, ejection fraction; and ESV, end-systolic volume.

the observed treatment effect size and the statistical power of the study.

Most patients underwent MRI scanning, which is regarded the gold standard for assessing LV function. Similar to our results, de Jong et al[4] found that the beneficial effect of cell therapy on LV EF and infarct size disappeared, when MRI was used for quantitative imaging. In addition, both studies found that the baseline EF did not affect the improvement in LV function compared with time.[4] Also our data were consistent with a previous study, where serial cardiac MRIs of patients with reperfused first AMIs showed a gradual increase in LV EDV during the first year after the AMI.[22]

In contrast with previous meta-analyses[3,4] we did not assess infarct size at follow-up because the majority of trials did not measure infarct size before cell therapy; therefore, no change between baseline and follow-up could be reported. Instead, we added the maximal CK as a confounding factor that could influence the outcome because maximal CK is highly associated with infarct size.[24]

In contrast with previous meta-analyses, we found no association between the number of cells delivered and the outcomes. It should be mentioned, however, that the numbers of cells used for intracoronary cell therapy varied widely, even without considering trials that assessed the importance of cell number on the clinical or functional outcome.

Table 6. Impact of Baseline Ejection Fraction on Changes in Left Ventricular Parameter

Baseline Ejection Fraction		Changes in End-Diastolic Volume (Mean±SD)	Changes in End-Systolic Volume (Mean±SD)	Changes in Ejection Fraction (Mean±SD)
≥50%	Cell therapy (n=179)	14.6±35.2	6.3±26.5	2.2±8.3
	Controls (n=145)	10.6±29.5	4.0±19.8	0.7±8.7
	Difference in mean between cell therapy and controls (95% CI)	4.0 (–3.2 to 11.2)	2.2 (–3.0 to 7.5)	1.5 (–0.4 to 3.3)
<50%	Cell therapy (n=445)	15.2±42.1	4.5±34.7	4.1±9.9
	Controls (n=295)	15.5±35.2	4.9±30.5	3.5±9.0
	Difference in mean between cell therapy and controls (95% CI)	–0.3 (–6.1 to 5.6)	–0.5 (–5.4 to 4.4)	0.6 (–0.8 to 2.0)
≥45%	Cell therapy (n=267)	11.1±34.8	4.2±26.5	2.3±9.0
	Controls (n=212)	9.7±29.6	2.9±20.8	1.3±8.7
	Difference in mean between cell therapy and controls (95% CI)	1.4 (–4.5 to 7.39)	1.3 (–3.1 to 5.6)	1.0 (–0.6 to 2.6)
<45%	Cell therapy (n=357)	18.1±43.6	5.6±36.4	4.5±9.8
	Controls (n=228)	17.9±36.4	6.2±32.4	3.8±9.0
	Difference in mean between cell therapy and controls (95% CI)	0.2 (–6.7 to 7.1)	–0.6 (–6.5 to 5.2)	0.7 (–0.8 to 2.3)
≥40%	Cell therapy (n=381)	12.1±36.8	4.0±27.1	2.6±9.2
	Controls (n=292)	10.8±31.0	3.3±22.6	1.9±8.5
	Difference in mean between cell therapy and controls (95% CI)	1.4 (–3.9 to 6.6)	0.7 (–3.1 to 4.6)	0.8 (–0.6 to 2.2)
<40%	Cell therapy (n=243)	19.7±44.7	6.5±39.7	5.0±9.7
	Controls (n=148)	202±37.2	7.3±35.1	4.1±9.6
	Difference in mean between cell therapy and controls (95% CI)	–0.5 (–9.2 to 8.2)	–0.8 (–8.7 to 7.1)	0.9 (–1.1 to 2.9)

No significant difference between the groups. CI indicates confidence interval.

Previous studies reported only the mean or median numbers of injected cells/group. Therefore, the results of those analyses should be considered less exact than results from this ACCRUE study.

One of the objectives of this meta-analysis was to reveal prognostic factors for clinical events or identify patients who might benefit from cell therapy. We did not achieve this objective, despite the fact that intracoronary treatment arm of the ACCRUE database included large randomized studies (mean of 104 patients per study) with remarkably low between-trial heterogeneity, when compared with the previous largest reported meta-analysis.[3,4] Because we used common definitions of primary end points throughout the studies, the heterogeneity for clinical end points was 0% among studies. In contrast to previously published meta-analysis, which showed up to 87% heterogeneity among studies, our meta-analysis showed little or no heterogeneity among studies for continuous parameters of the secondary end points, ie, the heterogeneities were 0% for ΔEDV, 11% for ΔESV, and 48% for ΔEF. This highlighted the accuracy of a large-scale IPD-based meta-analysis in characterizing any potential effect in different clinical subgroups and its pivotal role in fully exploring the clinical relevance and adequacy of cell therapy for treating IHD. However, according to de Jong et al,[4] >30 000 patients should be included in a study to identify an effect of cell therapy, when mortality is ≈2%.

Advantages of the IPD-Based Meta-Analysis

This ACCRUE IPD-based meta-analysis overcame the major limitations of systematic reviews and conventional meta-analyses. Those approaches extract aggregated data from available publications according to a predefined study protocol, and the random effects are determined by calculating the weighted means (eg, relative risk) of randomized trials. Accordingly, publication-based meta-analyses must exclude some important trials, where group differences are expressed as the median and interquartile range (eg, BONAMI, HEBE, MYSTAR, REGENT). Online Table IV shows the heterogeneity among reports of LV functional data from studies that were not included in the ACCRUE database. All but 1 study (Ruan et al, Reference 47, in the Online Data Supplement) were included in a recent intracoronary cell therapy AMI meta-analysis.[4] When no original data were available, they recalculated the mean differences and 95% CIs or SDs with meta-analysis software and a standardized formula. Thus, these recalculated data were partially discrepant with the published or original data; eg, Plewka et al showed changes in EF from baseline to follow-up of 10±9% in the cell therapy group versus 5±8% in controls (Reference 35 in the Online Data Supplement); in contrast; the calculated random-effect meta-analysis data showed EF changes of 9±5.8% versus 5±4.9%, or 9±7% versus 5±3.4% in cell-treated versus control groups, respectively.[3,4] In contrast, the present IPD meta-analysis included raw data; thus, we could calculate accurate real means with SDs, mean differences with SEs and CIs; moreover, these calculations were not influenced by the limited information gained from the publications.

Limitations of the ACCRUE Database

A major limitation of the presented study was the combination of several different cell types (bone marrow mononuclear cells, CD133+ -enriched bone marrow–derived cells or CD34+CXCR selected cells, or cardiosphere-derived cells). As in all previous meta-analyses, we assumed that the potency was comparable among different cell types. In fact, different cell population exert heterogeneous effects, depending on the amount of time passed since AMI.[23] In addition, when various clinically used cell types were compared directly in the same mouse infarct model, the rank order of efficacy was cardiosphere-derived cells>>bone marrow mononuclear cells.[25] Only 2% of the ACCRUE database comprised heart-derived cells; thus, heart cells were not well-represented in the present analysis. In addition, intracoronary infusion of allogeneic mesenchymal stem cells resulted in a 6.28% increase in EF, as reported by de Jong et al.[4] Our meta-analysis contained only studies with autologous cells, which in turn, increased its homogeneity.

Another limitation was that the ACCRUE database included fewer studies and patients than the total number of available published studies. Thus, this study did not include all studies that would be typically incorporated into a conventional meta-analysis. This lack was partly because of the resistance from centers to provide individual data, and partly because of the temporary closure of the database, which precluded studies that were published later.

Most previous large medical IPD-based meta-analysis studies were company sponsored. Those studies implemented a generalized electronic case report form, and the database and data were monitored by external monitoring companies. Therefore, extraction of standardized data from case report forms was a priori facilitated. However, to date, no company-sponsored studies on cell-based cardiac regeneration with intracoronary cell delivery have been conducted and controlled centrally. To date, no financial support was available for the effort of providing and formatting data in accordance with the ACCRUE database. In addition, data that did not represent the entire population could not be assessed, such as medication during follow-up, or data on stent thrombosis. However, the statistical analysis revealed a remarkably low heterogeneity across the trials in this ACCRUE study (I^2, 0% to 48%), compared with previous, largest meta-analyses (I^2, up to 87%),[3,4] because of the prespecified baseline and outcome parameters.

The results of this IPD meta-analysis revealed some important discrepancies from previous meta-analyses. Our findings highlighted the lack of consistent efficacy in cell-based cardiac regeneration with intracoronary delivery in patients with diverse cardiovascular risk factors. Although the ACCRUE database continues to recruit data, it cannot replace large-volume, prospective randomized studies, such as the ongoing BAMI trial (ClinicalTrials.gov Identifier: NCT01569178) or the CCTRN network.[26,27]

Appendix

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Disclosures

None.

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Novelty and Significance

What Is Known?

- Previous meta-analyses of randomized, cardiac cell-based therapy studies have shown moderate, but significant improvements in clinical outcome and left ventricular function.
- Those meta-analyses suggested that the beneficial effects were gained by increases in the number of cells delivered, by timing cell therapy for delivery 5 to 8 days post–myocardial infarction, or by selecting patients with decreased ejection fraction.

What New Information Does This Article Contribute?

- These meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) represent the first prospective meta-analysis in this field to be based on individual patient data (IPD), rather than on the aggregated data used in conventional meta-analyses.
- These IPD-based meta-analysis of randomized studies found that intracoronary administration of autologous reparative cells had no effect on major adverse cardiac and cerebrovascular events or on left ventricular performance or remodeling.
- Our results were not influenced by the timing of cell therapy, by the number of injected cells, or by the baseline cardiac ejection fraction.

This meta-analysis was based on a collaborative, multinational database (ACCRUE) that comprised IPD from randomized and cohort studies. The ACCRUE database was established to facilitate explorations of the clinical safety and efficacy of cell therapy in patients with ischemic heart disease and to identify subgroups of patients predicted to benefit from cell therapy. The ACCRUE database represents the most comprehensive source of evidence available to date. The present prospective study was the first to analyze data in the ACCRUE database on patients with recent acute myocardial infarctions. We included IPD from 12 randomized studies, and found that intracoronary autologous cell administration provided no benefit on overall clinical outcome. Moreover, we found no benefit on left ventricular performance or remodeling. Because the data pool comprised IPD, we could apply prespecified definitions of baseline and outcome parameters that accommodated multiple points of view and represented both clinical and functional end points. We tested the stability of these clinical and quantitative end points in several sensitivity analyses and found consistent results. This approach provided robust and justified conclusions.

SUPPLEMENTAL MATERIAL

Gyöngyösi. IPD meta-analysis of cell studies

Supplemental Methods

The ACCRUE Study is organized as follows: Independent Data Committee: Mariann Gyöngyösi (PI), Eliano Navarese (statistician) and Christer Sylven (data monitoring). Steering Committee: Wojciech Wojakowski MD, Patricia Lemarchand MD, Jozef Bartunek MD, Jens Kastrup MD and Douwe Atsma MD.

Additional study inclusion criteria for randomized studies

Additional inclusion criteria for the randomized AMI groups in the present analysis were: ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention, autologous cell-based therapy within 3 months after STEMI, intracoronary delivery of cells and a control arm that did not receive cells.

Due of the complexity of the database and the substantial differences between patients with recent AMI or ischemic cardiomyopathy, these two main patient subgroups were analyzed separately.

Search methods for identifying studies

The search methods for identifying studies were previously described in our recent review.[1] Briefly, we performed monthly searches on Medline, Google Scholar and Embase databases, and of the www.clinicaltrials.gov homepage for trials and manuscripts published recentl,y with the following search terms, alone or in combination: “cardiac stem cell”, “intracoronary stem cell”, “myocardial infarction”, “patient”, “percutaneous cell therapy”, and “myocardial ischemia”. Published abstracts and full-text articles written in English were reviewed. Studies were excluded when they presented only partial results of incomplete studies or meta-analyses[2-16] or when they presented only the abstract of a study or a sub-analyses of a previous report. Data from abstracts were not included, because they reported partial results or sub-analyses.

Data collection and management

We identified 55 published trials that applied cell therapy to induce cardiac regeneration in patients with ischemic heart disease (IHD). Data were extracted and entered on pre-specified forms by 2 independent investigators (JB, IP), who were not involved in any of the included studies. Internal validity was independently appraised by 2 investigators (MG, JB).

After data collection, the data were checked for inconsistencies, and the corresponding authors were contacted to clarify and correct the data. Where appropriate, the longest FUP time was chosen, when data were available, even when previous publications had reported shorter FUP time results. Data from cardiac MRIs, when available, were used for LV functional diagnosis; otherwise, contrast ventriculography, gated single photon emission computed tomography, or transthoracic echocardiography was applied.

When data proved to be compatible, they were transferred into the ACCRUE database.

Risk of bias and quality assessment of the studies

Data selection was primarily driven by the nature of the therapy, the ability of data to adequately fulfill the ACCRUE database objectives, the representativeness of the studies and the accessibility to the IPD of the studies. The quality assessment of the studies was performed in accordance with the Jüni criteria listing the internal validity parameter of the studies.[17]

Investigation of heterogeneity and selection bias

We also performed an overall meta-analysis with aggregate data from the included trials for the primary endpoint. Heterogeneity in pooled outcomes was assessed with the χ^2 test and I^2 statistic. The hazard ratio (HR) and 95% confidence intervals (CI) for the primary endpoint were

calculated.

Potential selection/publication bias was examined by constructing of a "funnel plot", in which the standard error (SE) of the ln HR was plotted against the HR for the primary endpoint. A mathematical estimate of the asymmetry of this plot was obtained with a linear regression approach.

Supplemental Results

Study quality and risk of bias in included studies

Supplementary Table I shows the quality assessment scales of studies in the ACCRUE database, that involved randomized intracoronary cell therapy in AMI.. The internal validity scales show that all studies allocated their patients adequately and that the treated and control groups were comparable; and all studies were conducted according to the intention-to-treat design. All trials reported a blinded analysis. External validity criteria were also adequate in all studies; they reported pre-specified patient characteristics, treatment regimens, levels of care, and outcome parameters. According to the pre-specified unified baseline and outcome parameters, the ACCRUE IPD meta-analysis results are more generalizable than the results of previous meta-analyses, therefore, a higher level of external validity was achieved with this meta-analysis *a priori*, compared to an aggregate data meta-analysis with heterogeneous definitions.

Sensitivity analyses were performed by removing one study at a time. This analysis demonstrated that no single study influenced the overall results; the effect estimates were consistent in magnitude and direction with the overall meta-analysis (data not shown).

Online Table I. Quality assessment scales for the randomized studies included in the "intracoronary cell therapy" arm of the ACCRUE database.

Bias	**Selection**			**Study Performance**	**Detection/ Evaluation**	**Attrition**
	Adequate allocation?	Method adequate for randomization?	Groups similar at start of the study?	Study patients/ staff blinded to study?	Study analysis blinded to randomization ?	Loss to follow-up (%)?
Cedars	yes	yes	yes	yes	yes	0%
Aalst	yes	unclear	yes	yes	yes	0%
BONAMI	yes	yes	yes	no	yes	0%
REPAIR-AMI	yes	yes	yes	yes	yes	0%
BOOST	yes	yes	yes	yes	yes	0%
LATE-TIME	yes	yes	yes	yes	yes	0%
ASTAMI	yes	yes	yes	no	yes	0%
REGENT	yes	yes	yes	no	yes	0%
SWISS-AMI	yes	yes	yes	no	yes	0%
TIME	yes	yes	yes	yes	yes	0%
SCAMI	yes	yes	yes	yes	yes	0%
FINCELL	yes	yes	yes	yes	yes	0%

Online Table II. Clinical end points using 9 supposed predictive factors

	Hazard ratio	lower 95% CI	upper 95% CI	p value
MACCE				
Cell treatment	0.826	0.581	1.175	0.287
Age	1.017	0.999	1.034	0.06
Gender	1.035	0.663	1.616	0.88
AMI anterior	1.257	0.764	2.069	0.369
DM	0.922	0.591	1.439	0.72
Hy	1.262	0.868	1.835	0.222
HLP	1.032	0.719	1.484	0.863
Pre-EDV	1.001	0.996	1.006	0.678
Pre-EF	0.994	0.976	1.012	0.52
Death				
Cell treatment	0.544	0.171	1.729	0.302
Age	1.087	1.017	1.161	0.014
Gender	0.855	0.243	3.011	0.807
AMI anterior	0.818	0.204	3.28	0.776
DM	1.497	0.438	5.116	0.52
Hy	1.21	0.335	4.369	0.772
HLP	0.352	0.1	1.243	0.105
Pre-EDV	0.992	0.977	1.008	0.325
Pre-EF	0.938	0.889	0.989	0.019
Death/AMI/Stroke				
Cell treatment	0.542	0.269	1.094	0.087
Age	1.0	1.01	1.085	0.012
Gender	1.106	0.461	2.653	0.821
AMI anterior	1.514	0.492	4.658	0.47
DM	1.036	0.457	2.346	0.933
Hy	1.83	0.812	4.122	0.145
HLP	0.713	0.35	1.455	0.353
Pre-EDV	0.998	0.989	1.007	0.684
Pre-EF	0.966	0.934	0.999	0.045
TVR				
Cell treatment	0.841	0.571	1.239	0.381
Age	1.01	0.991	1.029	0.307
Gender	0.988	0.604	1.615	0.96
AMI anterior	1.216	0.707	2.09	0.479
DM	0.871	0.526	1.44	0.59
Hy	1.18	0.783	1.777	0.43
HLP	1.159	0.775	1.732	0.473
Pre-EDV	1.003	0.997	1.008	0.32
Pre-EF	1.002	0.982	1.023	0.844

CI: confidence interval, MACCE: major adverse cardiac and cerebrovascular events, AMI: acute myocardial infarction, DM: diabetes mellitus, Hy: Hypertension, HLP: hyperlipidaemia, EDV: end-diastolic volume, EF: ejection fraction, TVR: target vessel revascularization
Significance if $p<0.01$

Online Table III. Detailed results of the Analysis of Covariance (ANCOVA).

		Changes in EDV		Changes in ESV		Changes in EF	
		Mean value (SE)	**95% CI**	**Mean value (SE)**	**95% CI**	**Mean value (SE)**	**95% CI**
Cell therapy effect with male gender	Cell therapy (n=511)	12.4 (1.7)	8.6, 16.3	4.0 (1.6)	0.9, 7.2	4.0 (0.5)	3.1, 5.0
	Control (n=375)	12.7 (2.5)	7.8, 17.7	4.1 (2.0)	0.0, 8.2	2.7 (0.6)	1.5, 3.9
Cell therapy effect with diabetes mellitus	Cell therapy (n=85)	16.0 (2.19)	11.7, 20.3	6.0 (1.8)	2.5, 9.5	3.16 (0.54)	2.1, 4.22
	Control (n=70)	13.7 (2.45)	8.9, 18.5	4.9 (2.0)	0.98, 8.8	2.46 (0.6)	1.28, 3.63
Cell therapy effect with hypertension	Cell therapy (n=303)	15.1 (1.5)	12.1, 18.0	5.0 (1.2)	2.6, 7.4	3.6 (0.37)	2.8, 4.3
	Control (n=218)	13.8 (1.8)	10.3, 17.3	4.7 (1.5)	1.8, 7.5	2.6 (0.4)	1.7, 3.5
Cell therapy effect with hyperlipid-emia	Cell therapy (n=316)	17.6 (1.6)	14.5, 20.7	7.0 (1.3)	4.5, 9.5	3.15 (0.38)	2.4, 3.9
	Control (n=206)	15.6 (1.9)	11.9, 19.4	6.4 (1.6)	3.3, 9.4	2.06 (0.46)	1.7, 3.0
Cell therapy effect with MRI	Cell therapy (n=425)	15.0 (1.62)	11.8, 19.2	4.3 (1.3)	1.7, 6.9	3.88 (0.4)	3.1, 4.7
	Control (n=240)	13.8 (1.8)	10.2, 17.3	4.6 (1.5)	1.7, 7.5	2.56 (0.44)	1.7, 3.4
Cell therapy effect with age	Cell therapy (n=624)	**23.8 (2.1)***	**19.7, 28.0**	11.2 (1.8)	7.6, 14.8	2.58 (0.924)	1.17, 4.0
	Control (n=440)	**14.4 (2.7)**	**9.1, 19.6**	4.7 (2.3)	0.2, 9.2	2.23 (0.578)	1.09, 3.36
Cell therapy effect with	Cell therapy (n=528)	15.1 (2.1)	10.9, 19.2	3.4 (1.7)	-0.0, 6.7	3.98 (0.52)	2.96, 5.0

AMI anterior

	Control (n=376)	16.2 (2.6)	11.2, 21.2	5.4 (2.1)	1.3, 9.5	2.51 (0.64)	1.26, 3.76
Cell therapy effect with pre-EDV	Cell therapy (n=624)	16.5 (1.1)	14.2, 18.7	5.8 (0.98)	3.8, 7.7	3.4 (0.41)	2.6, 4.3
	Control (n=440)	15.0 (1.3)	12.4, 17.7	5.5 (1.2)	3.2, 7.8	2.7 (0.49)	1.7, 3.7
Cell therapy effect with pre-EF	Cell therapy (n=624)	18.0 (1.3)	15.4, 20.7	7.04 (1.3)	4.5, 9.5	3.25 (0.48)	2.3, 4.2
	Control (n=440)	16.3 (1.6)	13.2, 19.5	6.5 (1.5)	3.6, 9.4	2.49 (0.57)	1.4, 3.6
Cell treatment effect with time to cell therapy[+]	Cell therapy (n=624)	13.5 (2.5)	8.6, 18.3	4.8 (2.0)	0.9, 8.8	2.7 (0.6)	1.6, 3.9
	Control (n=440)	5.7 (4.3)	-2.7, 14.0	-4.1 (3.5)	-10.9, 2.7	3.5 (1.0)	1.4, 5.5

***p<0.01**

CI: confidence interval, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, AMI: acute myocardial infarction, MRI: magnetic resonance imaging

[+]Effect of the covariate time to cell therapy in cell therapy group or randomization/sham intervention in controls post AMI

Online Table IV. Mean values and SD of changes of ejection fraction (EF) in patients with intracoronary cell therapy post-AMI (n=486; mean number of patients: 26±16) and corresponding randomized controls (n=351; mean number of patients: 18±15) of 19 trials not participating in the ACCRUE database.

Intracoronary cell injection	FUP time	Number of patients	Changes in EF from baseline to FUP mean±SD	Number of controls	Changes in EF from baseline to FUP mean±SD	Comments
Ge[29]	6 mo	10	4.8	10	3.5	*a*
Janssens[30]	4 mo	30	3.4±6.9	30	2.2±7.3	
Penicka[31]	4 mo	14	15.4	10	20.5	*a*
Meluzin[32]	3 mo	44	2±1 and 5±1	22	2±1	
Suarez[33]	3 mo	10	20±8	10	6±10	
Noguira[34]	6 mo	14	6.7±5.5	6	2±11.5	*b*
Plewka[35]	6 mo	38	10±9	18	5±8	
Cao[36]	6 mo	41	9.4	45	7.1	*a*
Yao[37]	12 mo	27	NA	12	2.9±2	*c*
Grajek[38]	6 and 12 mo	31	NA	14	NA	*a*
Piepoli[39]	12 mo	19	13.1±1.9	19	5.3±2	
Hirsch[40]	4 mo	67	3.8±7.4	60	4.0±5.8	*d*
Turan[41]	3 mo	42	NA	20	NA	
Liepic[42]	6 mo	26	3±7.3	10	3.8±4.6	
Quyyumi[43]	6 mo	11	2.5±9	10	1±7.8	*e*
Colombo[44]	12 mo	10	3±2.7	5	-3±3.9	*f*
Chen[45]	3 mo	34	NA	35	NA	*a*
Houtgraaf[46]	6 mo	9	4.6	4	NA	*g*
Ruan[47]	6 mo	9	NA	11	NA	*a*

SD: standard deviation, AMI: acute myocardial infarction, FUP: follow-up, EF: ejection fraction, NA: data not available

Comments:
a: SD of changes at FUP were not reported;
b: 10 patients received retrograde intravenous cell therapy; separate SD of changes were not reported;
c: data of repeated intracoronary injection of cells 3 months post-AMI in Group B were pooled to the single injection Group A, but significant difference between Group A and B was reported.
d: patients with intracoronary infusion of peripheral blood mononuclear cells are not included
e: dose escalation study with 3 different doses
f: data of bone marrow (Group A) and peripheral blood mononuclear cells (Group B) were pooled
g: 3:1 randomization of 14 patients with 1 drop-out; SD of changes in cell therapy group not available, no data of changes in EF in control group

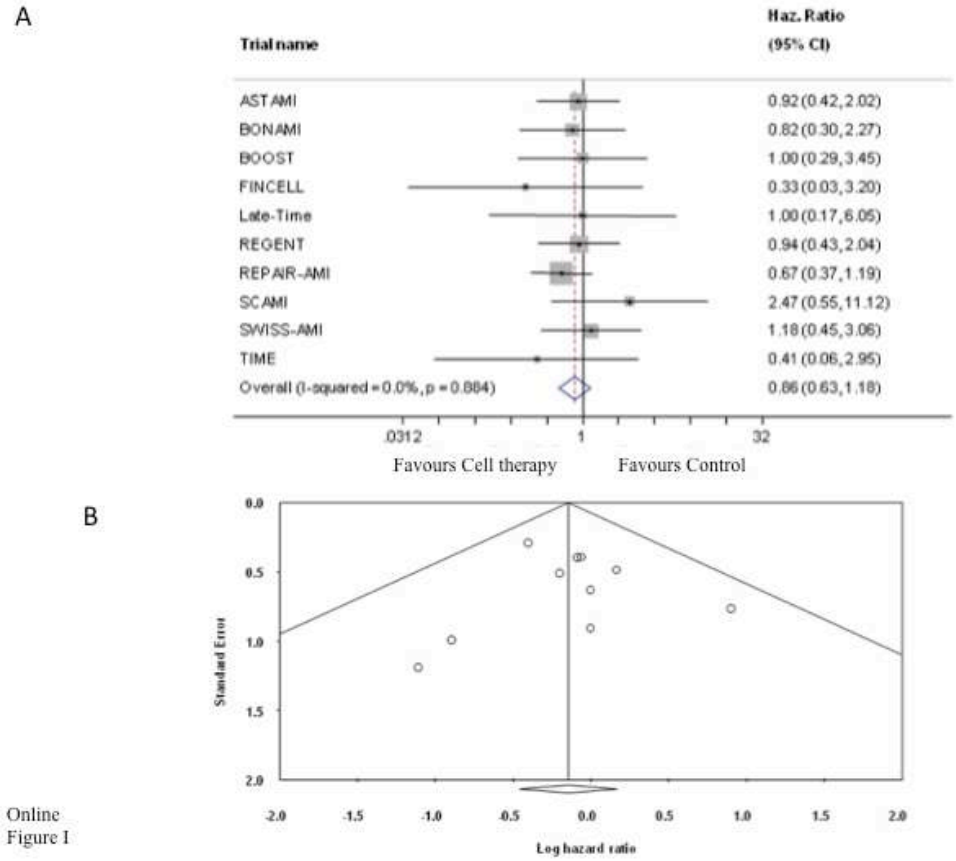
Online Figures

Online Figure I. Overall meta-analysis of aggregate trial data in the included studies for the primary endpoint of major adverse cardiac events, defined as death, re-infarction, stroke and target vessel revascularization.

Data in this table are based on the standard life table (first event per patient) computation. Individual papers contributing data to these tables may have used a different analysis plan and have reported their events differently.

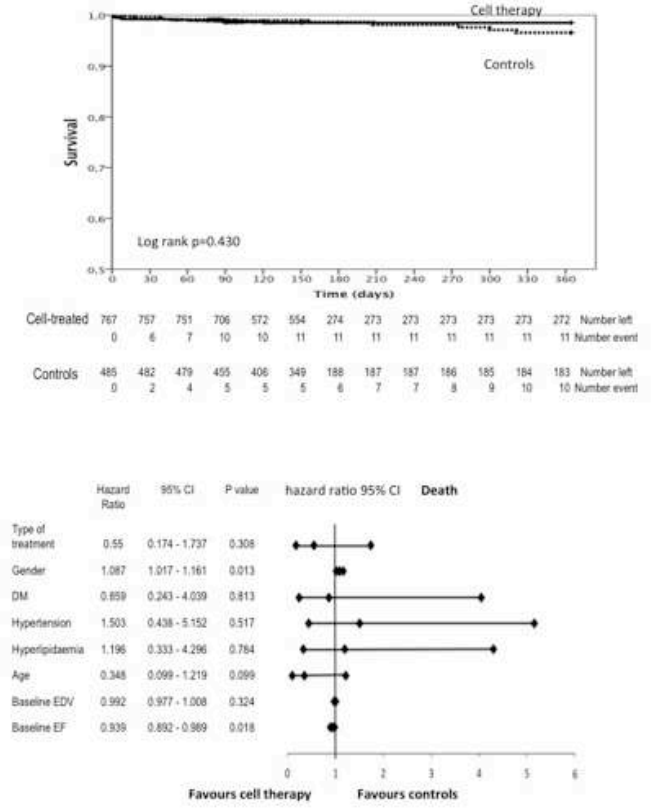
A. Meta-analysis of aggregate data
B. Funel plot

CI = confidence interval. Aggregate data from Aalst trial were not generated owing to the lack of primary endpoint events in both arms and the small sample size.



Online Figure I

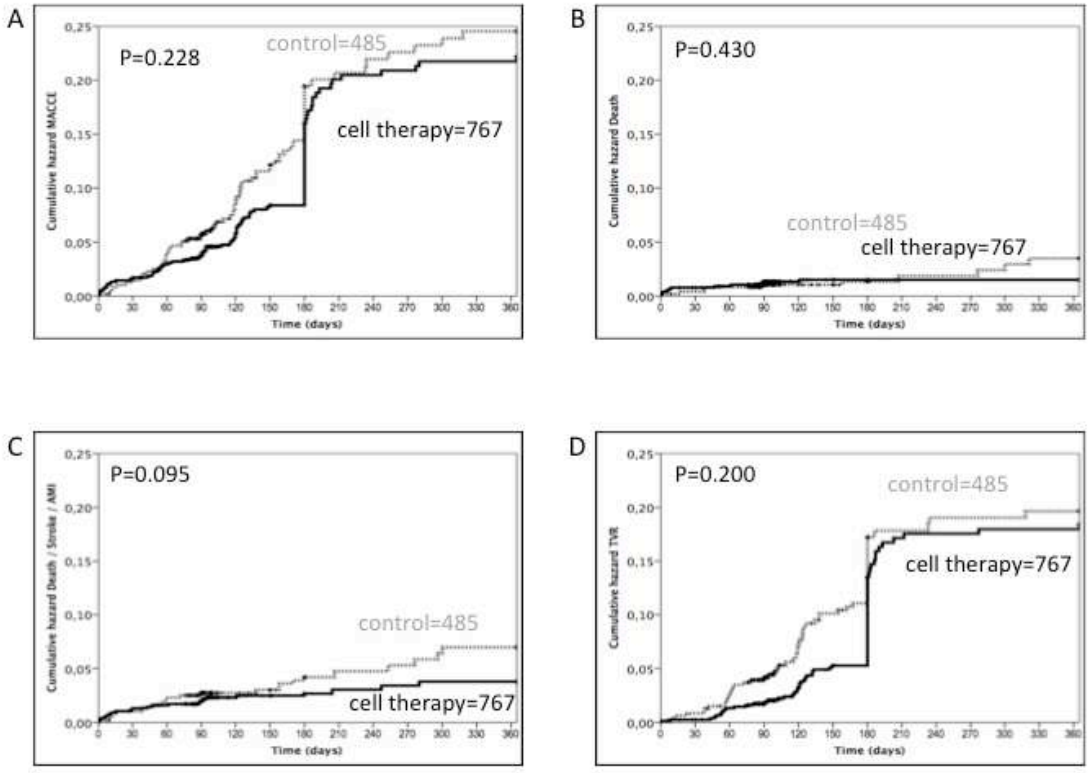
Online Figure II. Kaplan-Meier survival and Cox regression analysis of freedom from death
DM: Diabetes mellitus, CI = confidence interval



Online Figure II

Online Figure III. Cumulative hazards of clinical events of all patients. No difference between the groups.

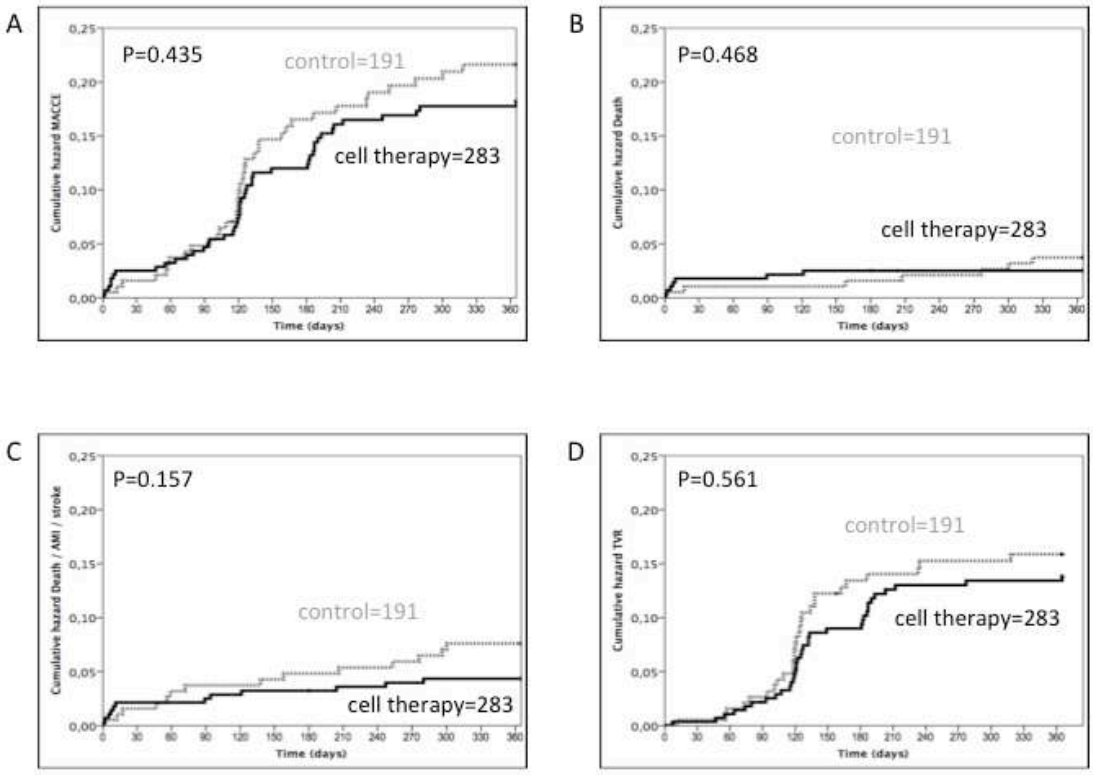
A. Cumulative hazard of major adverse cardiac and cerebrovascular events (MACCE)
B. Cumulative hazard of death
C. Cumulative hazard of death / re-myocardial infarction (AMI) / stroke
D. Cumulative hazard of target vessel revascularization (TVR)



Online Figure III

Online Figure IV. Cumulative hazards of clinical events in subgroup of patients with >6 -12 month control. No difference between the groups.

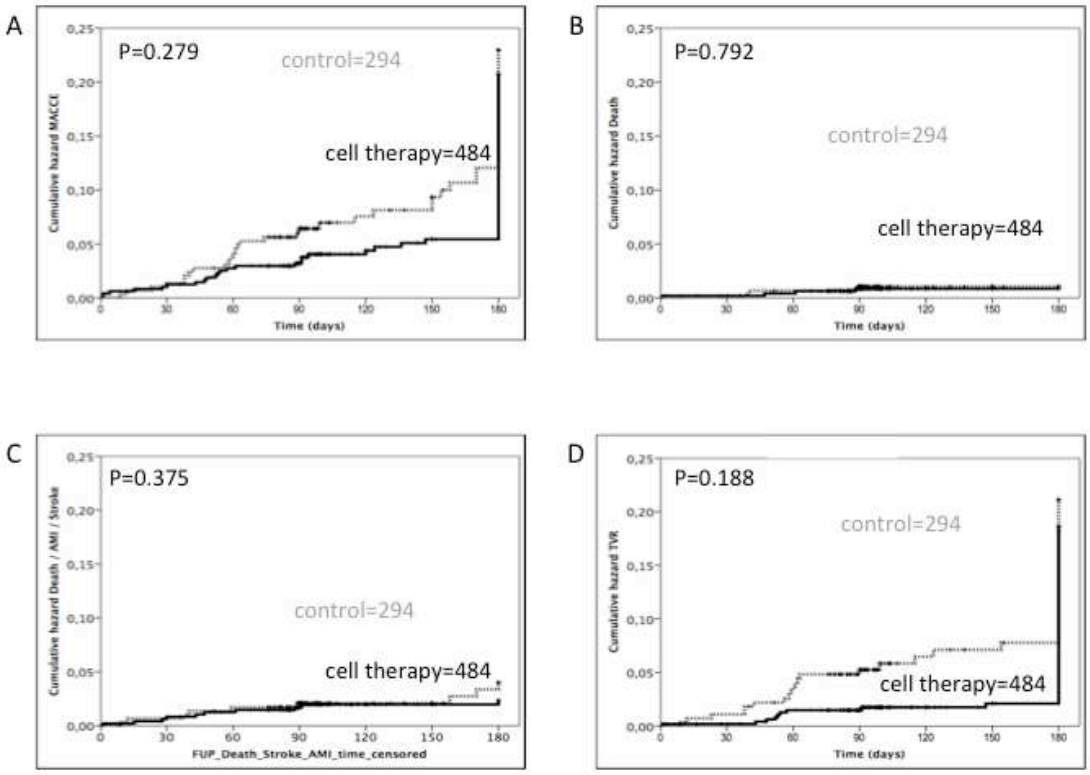
A. Cumulative hazard of major adverse cardiac and cerebrovascular events (MACCE)
B. Cumulative hazard of death
C. Cumulative hazard of death / re-myocardial infarction (AMI) / stroke
D. Cumulative hazard of target vessel revascularization (TVR)



Online Figure IV

Online Figure V. Cumulative hazards of clinical events in subgroup of patients with ≤ 6 months control. No difference between the groups.

A. Cumulative hazard of major adverse cardiac and cerebrovascular events (MACCE)
B. Cumulative hazard of death
C. Cumulative hazard of death / re-myocardial infarction (AMI)/ stroke
D. Cumulative hazard of target vessel revascularization (TVR)

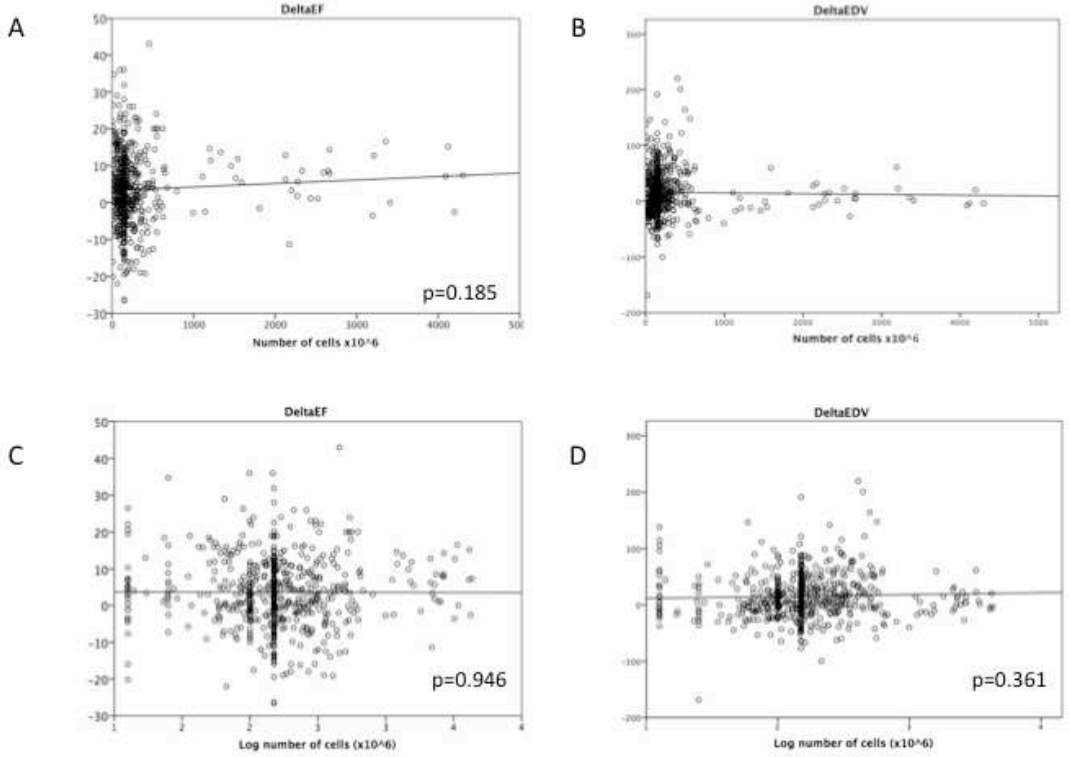


Online Figure V

Online Figure VI. Correlation between the number of intracoronary delivered cells and changes in ejection fraction (DeltaEF) and end-diastolic volume (DeltaEDV)

Lack of correlation was probably due to the large scatter in cell numbers.

A. Correlation between number of injected cells and changes in left ventricular EF
B. Correlation between number of injected cells and changes in left ventricular EDV
C. Correlation between log number of injected cells and changes in left ventricular EF
D. Correlation between log number of injected cells and changes in left ventricular EDV



Online Figure VI

Online References

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